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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,900	02/24/2004	Eugene R. Cooper	029318-1003	1015

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EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
09/29/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,900	COOPER ET AL.	
	Examiner	Art Unit	
	SUSAN TRAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-3,6-8,16,18-52,55-57,64-72,87,88 and 90-105* is/are pending in the application.

5a) Of the above claim(s) *26-49* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3,6-8,16,50-52,55-57,64-67,87,88 and 90-105* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/10/11 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 105 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 105 is rejected because it is not quite clear whether components (a), (b), (c) are all present in the dosage form, or whether the components are present in the dosage form alternatively.

Claim Rejections - 35 USC § 103

Claims 1-3, 6-8, 16, 50-52, 55-57, 64-67, 87, 88, 90-97, 101, 104 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struengmann et al. WO 99/09988 A1, in view of Liversidge et al. WO 9325190 a1.

Struengmann teaches a pharmaceutical composition comprising micronized meloxicam with suitable additive such as microcrystalline cellulose and/or surfactant and/or co-solvent (page 3; and examples). Surfactant is disclosed at page 4, last paragraph bridging page 5. Co-solvent includes propylene glycol, polyethylene glycol, glycerol and ethanol (page 3, last paragraph). The obtained meloxicam is then incorporated into dosage forms include controlled release oral composition, tablet, sachet, ointment, suppositories, and hydrogel (page 5, paragraphs 35).

Struengmann does not expressly teach the particle diameter of the micronized meloxicam. However, one of ordinary skill in the art would have been motivated to, by routine experiment optimize the particle size with the expectation of at least similar results. This is because it is known in the art to reduce particle size of a drug to obtain a higher bioavailability of said drug. Liversidge teaches a process of preparing nanoparticulate drug substances comprising the steps of dispersing a crystalline drug in a liquid dispersion medium containing a surface modifier, and subjecting the premix to mechanical means to reduce the particles size of the drug substance to less than 400 nm (pages 7-10). Drug includes water-insoluble drug substance such as analgesic and NSAID substances including oxicam (page 3). Surface modifier includes nonionic, anionic, organic, inorganic excipients, and mixture of two or more (pages 5-6). Surface

modifier includes polyvinyl pyrrolidone (page 6). Liversidge further teaches the surface modifier is adsorbed on the surface of the drug substance, but the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages (page 6, lines 25-31). Liversidge also teaches the nanoparticles are combined with pharmaceutically acceptable carrier suitable for parenteral injection (page 11, lines 29-35).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the meloxicam composition of Struengmann to obtain a nanoparticulate meloxicam composition in view of the teachings of Liversidge. This is because Liversidge teaches a nanoparticulate composition that exhibits unexpectedly rapid onset (bioavailability) (page 12, lines 11-14), because Liversidge teaches a process suitable for a wide variety of NSAIDs including oxicam, because Struengmann teaches the desirability for obtaining a composition with high bioavailability, and because Struengmann teaches reducing particle size of meloxicam by micronisation (page 3, last paragraph; page 10; and examples).

It is noted that Struengmann does not explicitly teach the claimed properties such as the C_{max} values. However, it would have been obvious to one of ordinary skill in the art to, by routine experimentation obtain the C_{max} value that falls within the claimed range, because Liversidge teaches nanoparticulate having the claimed particle size in a dispersion for parenteral injection exhibits the claimed C_{max} value, e.g., 187 µg/mL (page 16).

Claims 18-25, 68-72 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struengmann et al. in view of Liversidge et al., and Desai et al. WO 01/45706 A1 or Courteille et al. US 5,384,124.

Struengmann is relied upon for the reasons stated above. Struengmann does not teach the second particle population.

Desai teaches a dual-release composition of low water soluble drug (COX-2 inhibitor) comprising first fraction of the drug in nano-particulate form having average diameter of about 200 to about 400 nm and a D90 particle size less than about 5 μm (page 18); and a second fraction of the drug in micro-particulate form having D_{10} particle size of between 25 to about 100 μm (page 20, 1st paragraph). The first fraction nano-particle drug can be present alone or in combination with one or more excipient, such as nano-particles of the drug have a surface modifying agent (PEG-400) adsorbed on the surface thereof (page 18, 3rd through page 19). The weight ratio of the first to the second fraction of the drug in the composition is about 1:10 to about 10:1 (page 22, 3rd paragraph). The composition can be in an oral dosage form including tablet, pills, hard or soft capsule, lozenges, cachets, dispensable powder, granule, suspension or elixir (pages 37-38).

Courteille teaches a solid unitary composition comprising combination of nano-particle having diameter of less than 1 μm and micro-particle having diameter of between 1 μm to 2 mm (see abstract, column 2, lines 32-46). The mixture of nano/micro-particle contains one or more active agents of the same or different type (column 1, lines 66-68, and column 2, lines 23-31). The active agent can be selected

from antibiotic, analgesic, tranquilizer, vitamins, and therapeutic agents for diseases of allergies, hormones, or gastrointestinal tract (column 5, lines 46-66). The mixture of nano/micro-particle is prepared by any known method (air-fluidized bed coating, turbine coating, simple extrusion, or micro-encapsulation) employing the use of a polymer or a macromolecular substance (surface stabilizer) selected from the group of cellulose derivatives, starch, polyamide, collagen, dextrin, gelatin, polyvinyl chloride or the like (column 2, lines 46-55, and column 3, lines 18-40). The mixture further comprises stabilizing agent, surfactant, and biding agent (column 4, lines 20 through column 5, lines 1-28). Courteille further teaches the solid dosage form comprises immediate release with a secondary controlled release of mixture of nano/micro-particle (column 6, lines 16-50). The solid dosage form is to be incorporated into pharmaceutical oral dosage form (column 6, lines 51-56).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Struengmann to include the second particle population in view of the teachings of Desai or Courteille, because Desai and Courteille teach compositions suitable for analgesic substance, because Desai and Courteille teach that combination of one or more population of active substance with different particle size is well known in the art, and because Struengmann teaches the desirability for formulating a controlled release composition comprising different layer having different release profiles (page 5, 3-4 paragraphs).

Claims 1-3, 6-8, 16, 50-52, 55-57, 64-67, 87, 88, 90-97 and 101-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struengmann et al. WO 99/09988 A1, in view of Liversidge et al. WO 9325190 A1, and Cunningham et al. US 20040018242 A1.

Struengmann is relied upon for the reasons stated above. Struengmann does not expressly teach the claimed surface stabilizer such as sodium deoxycholate.

Cunningham teaches a nanoparticulate formulation comprising one or more surface stabilizer such as sodium deoxycholate and polyvinylpyrrolidone (paragraphs 106-107; claims 13, 48 and 69). Cunningham further teaches that surface stabilizers useful herein do not chemically react with the drug particle, and that the individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages (paragraph 0094).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include sodium deoxycholate as a surface stabilizer in view of the teachings of Cunningham. This is because Cunningham teaches the use of sodium deoxycholate and/or polyvinylpyrrolidone as a surface stabilizer is known in the art, and because Struengmann teaches the desirability for including surfactant such as polyvinylpyrrolidone.

Response to Arguments

Applicant's arguments filed 06/10/11 have been fully considered but they are not persuasive.

The Declaration under 37 CFR 1.132 filed 06/10/11 is insufficient to overcome the 103 (a) rejections based upon Struengmann et al. in view of Liversidge et al. as set forth in the last Office action for the following reasons:

1) with respect to the stability, Table 1 does not show a comparison data;

2) Table 2 only shows compositions with specific narrow particle size range of about 100 nm while the present claims recite particle size of less than 2000 nm, which includes particle size ranges from about 100-2000 nm;

3) it appears that Table 2 is not comparing similar compositions, such that it compares compositions with particle size of about 100 nm to MOBIC® with particle size of less than 10 μm (10,000 nm); and

4) the compositions in Table 2 comprise Poloxamer as a surface stabilizer, which is not recited in the claims.

As such the Declaration is insufficient to overcome the 103(a) rejections over Struengmann, in view of Liversidge.

Applicant argues that there is no reason to modify Struengmann's composition in view of Liversidge because Struegmann's teachings describe improving bioavailability by increasing the solubility of meloxicam. Struengmann disclosed that when a number of additives are mixed with meloxicam, the solubility of meloxicam is increased, as evidenced by the meloxicam dissolution data in the working examples. Although there is a very brief mention that meloxicam is micronized in the presence of co-solvents and hydrotropic agents, Struegmann fails to establish any correlation between particle size reduction and improving bioavailability. Further, Applicant argues that the proposed

goal of improving the bioavailability of meloxicam is already achieved by Struengrnann's teaching regarding mixing meloxicam with additives to increase the solubility of meloxicam. The skilled artisan would not have any reason to look to the secondary reference, Liversidge, to tackle a problem already solved by the primary reference.

However, in response to Applicant's argument that "a very brief mention that meloxicam is micronized in the presence of co-solvents and hydrotropic agents, Struegmann fails to establish any correlation between particle size reduction and improving bioavailability", the Examiner notes that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). In this case, Struegmann is relied upon for the teachings within the four-wall patent. Struegmann, throughout the patent, repeatedly teaches the desirability to reduce particle size of meloxicam by micronisation (page 3, last paragraph; page 10; and examples).

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case,

as discussed above, Struegmann teaches the desirability to reduce meloxicam particle size by micronization process. Liversidge teaches that in reducing the particle size of poorly soluble drug, the bioavailability is improved.

For at least the above reasons, the 103(a) rejections over Struegmann are maintained.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1615